Comments of J. Daniel Heck, Ph.D., DABT, Patricia Martin, Ph.D., DABT and Carr J. Smith, Ph.D., DABT, Scientific Affairs, for the Lorillard Tobacco Company

Preface

Comment on 6.2.1.2. Asthma induction in adults

The Cal/EPA 2003 draft report's conclusion that ETS exposure is causally associated with "adult-onset" asthma is at odds with the judgements of a number of authoritative scientific bodies that have recently reviewed available epidemiological data on this topic. Cal/EPA should seriously and objectively reconsider its conclusion in regard to "adult-onset" asthma causation to conform to contemporary standards for such scientific judgements.

Comment 1:

Cal/EPA's judgment is at odds with that of authoritative scientific bodies

The National Academies of Science' Institute of Medicine has very recently performed a thorough and exhaustive assessment of available evidence in regard to environmental factors that may cause or exacerbate asthma in adults and children (IOM – Clearing the Air 2000). The IOM report concluded that, among the many exposures considered, only house dust mite antigen had been demonstrated with sufficient evidence to cause the development of asthma. The IOM's consensus opinion in regard to ETS as a causative factor in the development of asthma in school-aged children, older children and adults was that there is *"...inadequate or insufficient evidence to determine whether or not an association exists..."* Similarly, IARC researchers had stated earlier (Tredaniel *et al*., 1994) that it "*..remains controversial..."* whether indoor air ETS is associated with chronic respiratory symptoms and asthma. Neither did the 1986 report of the US Surgeon General, the 1986 NRC report, nor the 1992 EPA report on ETS conclude that the evidence for ETS was sufficient to support a causal inference for "adult-onset" asthma.

Response:

There are number of reasons why the conclusions of the Cal/EPA differ from other evaluations, such as that published by IARC researchers in 1994 and the IOM in 2000. In the case of the association with asthma, we include some studies and meta-analyses that were unavailable to the IARC researchers and IOM at the time of their reports. This

includes an update of the OEHHA staff's meta-analysis of ETS and childhood new onset asthma. OEHHA staff and consultants also undertook different (and in some cases more extensive) analyses of than those used by IARC and others. .

Comment 2:

The remarkable Cal/EPA draft assertion that "adult-onset" asthma has been shown conclusively to be causally associated with ETS exposures falls far short of the standards for such scientific judgments and should be withdrawn in a draft revision.

The etiology of asthma is only *incompletely understood*, and is *far too complex* to justify a simplistic inference of causation from a limited number of inconsistent epidemiological studies having inadequate confounder adjustments and at best weakly positive statistical associations with indoor air ETS exposures.

A bewildering genetic heterogeneity underlies the development of asthma; the scientific literature contains hundreds of genetic association studies on asthma-related phenotypes, with variants in 64 genes reported to be associated with asthma or related traits in at least one study (*1*). None of the nine new studies cited in the Cal/EPA 2003 draft included consideration of this variable in the diverse study populations.

While the new epidemiological reports cited by Cal/EPA in support of a causal inference for "adult-onset" asthma in association with ETS exposure included some adjustments for confounders, none of the individual studies has come close to adequately considering the full spectrum of diverse associations that have emerged as potentially potent confounders for this complex disease. One example of such an emerging confounder is described in a very recent systematic review of extant literature that found that aspirin-induced asthma is detectable in fully 21% (14-29%, 95% C.I.) of adults when definitive oral provocation testing is conducted (*2*). Notably, only about 3% (2-4%, 95% C.I.) of adults in this analysis were aware of such aspirin sensitivity and reported it at interview. This recent observation documents the imprecision and limited utility of self-reported symptoms in diseases of extraordinarily complex etiology such as asthma, and indicates that simplistic inferences of causation based upon such data are unlikely to be correct. Among the new "adult-onset" asthma reports cited by Cal/EPA (2003), 7 of 9 studies employed unreliable self-reported asthmatic symptoms or self-reports of asthma diagnosis.

Notably, the two cited studies that included more objective physician-diagnosed asthma data (Kronqvist, 1999; Flodin, 1995) did <u>not</u> report statistically significant associations of asthma and ETS exposure.

Cal/EPA should objectively consider the available data on the unreliability of such self-reported asthma symptoms in drawing conclusions of causation that are at odds with

those made in previous and more rigorous assessments by other scientific and public health bodies.

Response:

Self-reported physician diagnosed asthma is a standard epidemiologic tool used to identify persons with asthma (Toraen et al., 1993; Dodge and Burrows, 1980; Dodge et al., 1986; Burrows et al., 1991). It has been shown to be reliable and valid (Toraen et al., 1993; de Marco et al., 2004). Definitions of asthma based on asthma symptoms and / or asthma medication use are also widely accepted epidemiologic tools that have notably been used in the highly regarded European Community Respiratory Health Survey (Basagana et al., 2004; Abramson et al., 1996; Neukirch et al., 1995; ECRHS 1995; Bjornsson et al., 1994; Jarvis et al., 1994; Burney et al., 1989; Burney et al., 1994).

Taken together, the studies have controlled for a broad array of potential confounding variables. One cannot exclude the possibility of residual confounding, of course, but it seems unlikely to explain these results. It is not valid to extrapolate the data from self-report of aspirin sensitivity to draw conclusions about self-report of asthma. Self-reported ETS exposure is likely to be more accurate than self-reported aspirin sensitivity, as ETS exposure is an obvious environmental entity whereas aspirin sensitivity is an immunologic phenomenon that may not be obvious to the subject. To argue that aspirin sensitivity is a confounder in the ETS-asthma relationship one would have to assume some association between aspirin sensitivity and asthma as well as an association between aspirin sensitivity and ETS exposure. There is no evidence nor reason to assume this that OEHHA is aware of and the commentator offers none.

Flodin did show increased risk, although the 95% CI included no effect which may be due to small sample size and lower statistical power; Kronqvist was a negative study as we acknowledged, but this was confined to a very select group, i.e., Swedish farmers. There is evidence that exposure during childhood to farming is protective (von Mutius 2002). Therefore, such exposure could obscure any adverse affects from ETS exposure; Jaakkola 2003 used a physician diagnosis and found a link between ETS and incident adult-onset asthma.

Comment 3:

Clinical studies of asthmatics exposed to experimental ETS have strongly suggested that reactions to ETS do not occur by the IgE-mediated mechanism that is a hallmark of classic allergic asthma (*16*). A minor subset of study subjects reporting ETS sensitivity and having clinically diagnosed asthma have been shown to react to experimental levels of ETS exposure with modest reductions in FEV_1. However, the detected responses appeared to be attributable largely to sensory irritation by constituents of the ETS gaseous phase and exhibited a clear exposure-response relationship for measurable effects in ranges far higher than those typically encountered (*16*).

Response:

These findings are restricted to acute responses that are more relevant to asthma exacerbation than to asthma induction. Longer-term effects from chronic lower levels of exposure such as airway remodeling and sensitization were not evaluated in the clinical study referred to in the comment.

Comment 4:

In the following text, the conclusions of Cal/EPA are addressed as summarized below:

1. Asthma is an exceedingly complex and incompletely understood disease; simplistic conclusions regarding its etiology, based upon weak statistical associations with environmental exposures, are at best tenuous.

2. The contention that ETS induces asthma in adults is supported by neither the weight and strength of available epidemiological evidence, nor by a compelling body of mechanistic evidence. No authoritative consensus judgement regarding causation of adult onset asthma by ETS has been made previously by any expert scientific/public health organization.

3. The entire body of available epidemiological data, including the nine new studies cited in the Cal/EPA 2003 document, is an entirely insufficient basis for a reasonable scientific conclusion of a causal association between ETS exposure and induction of adult asthma.

4. Major asthma risk factors include family history of atopic disease, atopy, exposure to house dust mites, cat dander, cockroach antigens and childhood obesity. The potentially confounding effects of these major asthma risk factors are difficult to control for in any epidemiological study.

5. ETS and respiratory health studies are difficult to conduct and interpret.

6. Real-world levels of ETS exposure, and particularly outdoor air levels, are trivially low.

7. The draft conclusion that ETS exposure causes "adult-onset" asthma is not consistent with contemporary scientific standards and should be withdrawn.

Response:

While we understand that good scientists and epidemiologists are appropriately reluctant to assign the term causative to an exposure without substantial and convincing evidence, we believe that indeed this hurdle has been cleared in the case of ETS and adult onset asthma. Some of the key factors are outlined below and our discussion has been expanded similarly in the revised document.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger et al. 1994), number of

smokers in the environment (Leuenberger et al. 1994; Hu et al. 1997), duration of exposure to smoker (Leuenberger et al. 1994; Kunzli et al. 2000; Iribarren et al. 2001; Janson et al. 2001), duration of working with a smoker (Greer et al. 1993; McDonnell et al. 1999), measured nicotine levels (Eisner et al. 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola et al. 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin 1995, Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999), or a defined period prior to the development of asthma-like symptoms (Withers 1998, Strachan 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed a positive association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related

respiratory health outcomes, including new-onset asthma and wheezing, supports a causal association between ETS exposure and adult onset asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (California Environmental Protection Agency 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biological plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole et al. 1989),(Comstock et al. 1981),(Ng et al. 1993),(Masi et al. 1988),(O'Connor et al. 1987)-(Xu and Li 1995) (Schilling et al. 1977; Kauffmann et al. 1989) (Brunekreef et al. 1985)-(Abbey et al. 1998; Carey et al. 1999) (Jaakkola et al. 1995) (Dimich-Ward et al. 1998) (Eisner et al. 1998; Eisner 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of ETS exposure and incident adult asthma (Thorn 2001, Hu 1997, Greer 1993,

McDonnell 1999, and Jaakkola 2003). Other studies have prospectively examined the relation between ETS exposure and incident wheezing (Withers 1998, Strachan1996). In addition, since the writing of the original draft of our document, a very useful paper has been published that provides the kind of gold standard evidence that has been difficult to obtain. This is a study in Finland by M. Jaakkola, et al (AJPH, 2003;93:2055-2060), which was a large population based incident case-control design in a system that had the advantage of being able to define all incident cases of new onset asthma diagnosis. Diagnosis was based on clinical examination and included lung function measurement. Recruitment was aided by being able to identify via National Social Insurance records all patients who had received reimbursement for asthma medications and included 521 newly diagnosed case patients out of a population of over 440,000. The risk of new onset asthma in adults age 21-63 was doubled in those exposed to workplace ETS (OR 2.16, CI 1.26, 3.72) and nearly five fold in those with home exposure (OR 4.77, CI 1.29-17.7). Cumulative exposure over a lifetime at work and at home increased risk. This study indicates that cumulative lifetime exposure to ETS increases the risk of adult-onset asthma. A summary of this paper is included in the revised document.

The population-based study by Jaakkola and colleagues provides the strongest corroborating evidence to date that ETS exposure causes adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the

entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of incident adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

Comment 5:

Major Asthma Risk Factors

Boushey *et al*. (2000) provide the following descriptions of asthma risk factors:

> "The strongest is a family history of atopic disease."
>
> "Atopy greatly increases the risk of asthma."
>
> "This has best been established for the house dust mite…Other allergen exposures linked to a heightened risk of asthma are cat dander, cockroach, …"

Response:

Comment noted. OEHHA agrees that these are important risk factors for asthma.

Comment 6:

"In Britain and the United States, the rise in asthma among children has been accompanied by an almost epidemic increase in the prevalence of obesity."

Response:

This is an ecological association and therefore is not able to identify whether obesity predates, is coincidental to or is a consequence of asthma. Therefore, this study has no ability to assess the relationship between obesity and asthma at the individual level or to impart new insight on the ETS-adult asthma onset link.

Comment 7:

A very recent longitudinal study of "adult-onset" asthma among members of a New England HMO found that new-onset asthma cases were overwhelmingly more likely to have occurred in association with infection than in association with workplace/environmental exposures (Sama *et al*., 2003).

Response:

This does not in any way affect the interpretation of data focusing on ETS and adult asthma. Viral infection is associated with asthma. However, asthmatics are more likely to suffer respiratory infections so infections may or may not predate the onset of asthma. If the study didn't determine the temporal relationship, then adjusting for infections could obliterate associations from other causes by 'over controlling', which would explain the findings by Sama et al.

Comment 8:

Therefore, it is very important in any ETS-asthma epidemiological study to account and adjust, fully and accurately, for the major risk factors for asthma. The available studies to date that are cited by Cal/EPA do not fully meet this requirement.

Response:

There is no evidence, uncovered by the OEHHA review nor is any evidence presented here in the comment, that the ETS-asthma onset association is explained by unmodeled confounding. Importantly, the evidence that obesity is a cause of asthma is speculative only, so confounding by obesity is unlikely. Multiple confounders are considered and adjusted for in studies from around the world and the preponderance of evidence points to a role of exposure to tobacco smoke in asthma causation.

Comment 9:

Difficulties In Conducting And Interpreting ETS And Respiratory Health Studies

ETS and Respiratory Health in Adults

Respiratory diseases and symptoms in either healthy or compromised adults exposed to ETS have not been as widely studied as they have been in children. No clear picture emerges from an analysis of the published papers on this subject, because the literature reports positive and negative associations as well as non-associations.

The ETS studies on adult respiratory health are influenced by many of the same potential confounders as the childhood studies, but there are at least 5 factors that may be of increased importance in considering design of ETS studies in adult populations: 1) Presence of adult lifestyle confounders (*e.g*., alcohol consumption, dietary habits, hobbies such as woodworking and ceramics, *etc*.). 2) Occupational exposures to lung irritants. 3) Difficulty in obtaining accurate lifetime medical histories. 4) Greater difficulty in estimating current and past ETS exposure because of the increased mobility of adults. 5) Increased possibility of psychological aversion to ETS, resulting in exacerbation of reported symptoms (Smith *et al*., 1992).

In addition to the potential confounders noted above, a number of possible biases are important considerations in ETS studies. These biases include misclassification of smokers as nonsmokers, reporting bias including recall bias, and diagnostic bias.

Response:

All epidemiologic studies are subject to the classes of bias listed above. However, nearly all studies included in the report appeared in high quality peer reviewed journals, and evaluation of all sources of bias is part of the review process. Many manuscripts are rejected based on factors that may have introduced too much bias into the studies. The studies included in this report were selected based on having met the standards of quality for conducting and reporting observational studies. Although no epidemiologic study can completely rule out bias, the consistency of results across many study designs conducted in multiple populations and locations around the world, it is unlikely that all studies suffer from a common systematic error. This consistency supports a causal

association between the risk factor and the disease. Those studies that more adequately accounted for bias and confounding were considered of higher quality in this review and were weighted accordingly.

Comment 10:

Analysis Of Nine Asthma Studies Not Considered In 1997 Cal/ Epa Document

The Cal/EPA 2003 draft report states that the 1997 OEHHA report reviewed studies evaluating the relationship between ETS exposure and chronic pulmonary disease among adults, including asthma. They concluded "… ETS exposure may make a significant contribution to chronic respiratory symptoms in adults." Although the OEHHA reported in 1997 on five studies purportedly supporting an association between ETS exposure and "adult-onset" asthma (Dayal *et al*., 1994; Greer *et al*., 1993; Leuenberger *et al*., 1994; Ng *et al*., 1993; Robbins *et al*., 1993) no specific conclusions were articulated about asthma *per se*. Cal/EPA 2003 presents nine recent epidemiological studies that evaluated the impact of ETS exposure on new-onset adult asthma and, remarkably, draws an affirmative causation conclusion.

The nine studies listed in Cal/EPA 2003 Table 6.14 have been reviewed and a summary of their design features is listed in Tables 1 and 2 with written comments following. Table 1 lists author/reference, study type, variables tested, population studied, and country. In addition, Table 1 summarizes criteria used to establish smoking status (smoker vs non-smoker), lab confirmation of smoking status, ETS exposure assessment, and known (established) home and occupational exposures/confounders. Where possible, Table 2 summarizes author definition of asthma and assessment/diagnosis of asthma. Categorizations include self-reported asthma or symptoms of asthma; self-reported physician diagnosed asthma; physician diagnosed asthma; and medical (clinical testing) confirmation of asthma.

An analysis of Tables 1 and 2 (attached) shows the inadequacies of the nine additional epidemiological studies regarding the purported contribution toward a conclusion of a causal association between ETS and adult onset asthma. For example, all nine studies rely on questionnaires, with only one study fully incorporating examination-based physician diagnosed asthma, and none fully confirm smoking status by laboratory test. In addition, only three of the nine studies are prospective in design, with the remainder being either cross-sectional or case control. Therefore, the study designs generally do not facilitate control for recall bias and preclude determinations of causality.

Cross-sectional studies are, in any event, inappropriate for the development of inferences of causation and temporal relationships between purported exposures and effects.

Response:

The determination of causation in the OEHHA report is made from the entirety of the evidence and not based on a single study or study design. Perhaps the most influential study to date is Jaakkola (2003) that restricted cases to incident adult asthma and used medical examination to establish a physician diagnosis of asthma. A clear association between adult onset asthma and exposure to ETS is found in this high quality study. Case control studies are not necessarily weaker designs than cohort studies, as they are all nested within a cohort (actually or theoretically). Adequacy of exposure assessment, generalizability of the study population, along with many other factors must be considered in determining study quality.

It is standard procedure to define smoking by self-report, and not by laboratory methods, in epidemiologic studies. For example, the centers for Disease Control and Prevention uses the National Health Interview Survey to estimate smoking prevalence in the United States based on self-reported smoking behavior (MMWR, 2004). Self-reported ETS exposure is the standard in the field of epidemiology for studying diseases with long induction periods such as asthma (Benowitz, 1999; Jaakkola and Jaakkola, 1997). Biomarkers, of which cotinine is the most common, have short half lives and have limited usefulness in study of the onset of diseases with long induction periods (Benowitz, 1999; Jaakkola and Jaakkola, 1997; Daisey, 1999). There are numerous studies that validate the use of self-reported ETS exposure (Coghlin et al., 1989; Coultas et al., 1989; Coultas et al., 1990; Cummings et al., 1990;Cunningham et al., 1996; Eisner et al., 2001; Emmons et al., 1996; O'Connor et al., 1995; Willemsen et al., 1997).

Comment 11:

Kronqvist et al., 1999

A large population-based cross-sectional study examined risk factors associated with asthma and rhinoconjunctivitis in 461 Swedish farmers. The farmers received a medical examination comprising a skin prick test (SPT), radioallergosorbent test (RAST) analyses, and lung function measurements. A questionnaire established symptoms and exposures. Subjects with a history of episodic shortness of breath, wheezing, and breathing difficulties were defined as having asthma. Allergen sensitization, especially to mites (OR=5.8 vs OR=3.8) and pollens (OR=10.3 vs OR=5.8) was significantly associated with asthma and rhinoconjunctivitis, respectively, in this farm community. Exposure to ETS in childhood and current exposure did not seem to affect the risk of allergen sensitization among either smokers or nonsmokers. No ETS data were given

Cal/EPA 2003

"By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. ETS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of ETS exposure, past or present, was associated with the risk of asthma (OR or RR were not reported) (Table 6.14)."

Heck et al. *Comments*

The study was relatively large and included 461 Swedish farmers receiving medical exam, SPT, RAST analyses and lung-function measurements. The authors noted the following: "Reported exposure to environmental tobacco smoke in childhood or currently did not significantly affect the risk of airway disease in smokers, ex-smokers, or nonsmokers."

Response:

It is unclear what is meant by the comment that "no ETS data were given" as ETS exposure was assessed for the current period (home and work) and during childhood. This is a negative study, but was confined to Swedish farmers. There is evidence that exposure during childhood to farming is protective (von Mutius 2002). Therefore, such exposure could obscure any adverse effects from ETS exposure. As noted above, OEHHA relied on a number of studies, not just a single study, in concluding there is adequate evidence of a causal association between ETS exposure and adult onset asthma.

Comment 12:

Iribarren et al., 2001

This large cross-sectional study examined *current* exposure to ETS and the association with personal characteristics and self-reported health conditions as determined from a multiphasic health check-up between 1979 and 1985. A total of 47,472 adult never-smoking members of the Northern California Kaiser Permanente Health Plan undergoing multiphasic health check-ups between 1979 and 1985 participated in the study. A written questionnaire was used to record duration and location of ETS exposure. Although it is not clear exactly when the ETS exposure data were collected it appears at least partially retrospective.

The authors conclude ETS exposure correlates with several personal characteristics potentially associated with adverse health outcomes. They state ETS exposure was associated with several self-reported acute and chronic conditions but that the study design precluded causal inference.

Cal/EPA 2003

“Using a written questionnaire, current ETS exposure was ascertained for several locations: home, other small spaces (e.g., office or car), and large indoor spaces (e.g., restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any ETS exposure was associated with a greater risk of self-reported physician-diagnosed asthma or hayfever (OR 1.22, 95% CI 1.11-1.34 and OR 1.14; 95% CI 1.06-1.24, respectively), controlling for socioeconomic and demographic covariates. The risk estimates were similar for high level exposure ($\geq$ 40 hours/week) compared to no exposure. For weekly exposure duration, there was evidence of an exposure-response relationship among women but not men.”

Heck et al. *Comments*

The authors noted the following limitations:

> "ETS exposure correlated with several personal characteristics potentially associated with adverse health outcomes."
>
> "Firstly, the design was cross-sectional, precluding temporal associations and inferences about cause and effect."
>
> "Thirdly, the assessment of medical conditions relied on self reports; no attempt was made to determine the sensitivity or specificity against a gold standard of care or serological markers."
>
> "Estimation of lifetime exposure to ETS ...was not possible in this cohort because duration of ETS exposure was not ascertained."

> "We found, unexpectedly, significantly lower odds of stroke among men reporting any ETS exposure at home or in large indoor areas."
>
> "Another noteworthy finding was the lack of association of self reported cancer or tumor with any source of ETS exposure individually or with total ETS exposure in either gender."

The manner in which the Cal/EPA draft presents its abbreviated review of the paper of Iribarren *et al*., (2001) is misleading in several respects, and should be revised to include and objectively discuss in their entirety the authors' peer-reviewed observations and conclusion that bear on whether ETS may be causally-associated with "adult-onset" asthma. These elements include the authors' admonition that cross-sectional studies such as that of Iribarren *et al*., (2001) cannot be legitimately employed to develop inferences of causation or temporal associations between environmental factors and the occurrence of "adult-onset" asthma.

The combination of "hay fever/asthma" for the purposes of this broad cross-sectional survey of health plan members unavoidably results in the combination of a variety of distinct disease conditions into a single symptom category. The selection of a few among the array of similarly weak and highly variable statistical associations among various lifestyle characteristics, behavioral traits, self-reported symptoms and ETS exposures reported in the original paper's Tables 4, 5 and 6 does not provide any reasonable basis for development of any conclusion of causation.

Response:

Causal inference cannot be based on a single study regardless of the study design. However, the consistency of results across several study designs, multiple populations and geographic locations supports causation. Iribarren (2001) corroborates the findings from cohort and case-control studies. This is a cross-sectional study, so ETS exposure was assessed at the same time as the health conditions. This is clearly stated in the report.

Iribarren et al. are correct to be cautious about causal inference from a single cross-sectional study. However, it is a very large study that is highly generalizable to the general U.S. population. Taken together with the other studies, it provides supportive

evidence that ETS exposure is associated with new-onset adult asthma. Including hay fever in the outcome definition could obscure the relationship between ETS exposure and asthma. This broader outcome definition is a limitation of the Iribarren et al study.

Comment 13:

Larsson et al., 2001

A population-based study examined the impact of "at home childhood ETS exposure" on current self-reported physician-diagnosed asthma during adulthood. The participants included 8008 randomly selected adult never smokers (age 15-69) from Sweden. A questionnaire (postal survey) was used to estimate exposures, airway symptoms, and respiratory history. The authors concluded that, "childhood exposure to ETS is associated with an increased prevalence of asthma among adult never-smokers, especially in nonatopic subjects. Children exposed to ETS were also more likely to become smokers. ETS is a major lower airway irritant (LAWI)."

Cal/EPA 2003

"The prevalence of adult asthma was more common among subjects who indicated childhood ETS exposure (7.6%) compared to unexposed persons (5.8%) (p=0.035). Current self-reported "breathing difficulties from cigarette smoke" were also more common among subjects who indicated a history of childhood ETS exposure. In further analysis, the authors stratified by family history of asthma. Although there was no clear impact of ETS among subjects without a family history of asthma, ETS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28-2.58). These results could be consistent with higher rates of smoking cessation by asthmatic's parents, reducing exposure of their children with asthma."

Heck et al. *Comments*

Self-reported ETS exposure was assessed by the question, "Do or did any of your parents/relatives smoke at home when you grew up?" All questions were answered as either "yes," "no," or "not as far as I know." ETS exposures from smoking by parents or other relatives who actually live in the house is very different from that by relatives who occasionally drop by and smoke in the home. Also, there is no estimate of degree/intensity of exposure that may have occurred. It is unclear whether the self-reported current asthma began in childhood or is "adult-onset." Therefore, the relevance of these results to "adult-onset" asthma are also unclear.

The authors note "The difference in asthma prevalence between subjects exposed and not exposed to childhood ETS was more pronounced in the younger half of the population." The effect of recently-increased awareness of purported adverse effects of ETS on the

accuracy or consistency of the reporting by younger subjects was apparently not considered as a potential source of bias in the study.

"Wheezing" is not reported as significantly associated with ETS exposure. In fact, the *p* value for wheezing is 0.792, although wheezing is a hallmark symptom of asthma.

Additionally, the authors state "We cannot exclude the possibility of reporting bias where asthmatics are more prone than nonasthmatics to report ETS exposure, which would give an overestimation of the risk" and "...the association between active smoking and asthma is uncertain in the current literature."

Response:

Results from Table 5 of the article by Larrson et al 1994 are consistent with those observed in the meta analysis of studies that examined ETS exposure and new-onset asthma in childhood. The risk was elevated and highly consistent among studies that controlled for allergic tendency and child's own smoking habits. Other results presented in the article are obscured by the lack of control for one or both variables.

The comment implies that the study age population was not relevant to the issues of "adult-onset" asthma. The majority of subjects were adults at the time of the study; all were older than 15 years. It is true that adult vs. childhood asthma onset cannot be completely distinguished, as the outcome was a lifetime history of physician diagnosed asthma. Childhood ETS exposure was also a risk factor for current wheezing and shortness of breath, supporting the contention that at least some of the ETS-related asthma onset occurred during adulthood.

The commentator was concerned about awareness on the part of some of the younger subjects of the health hazards associated with tobacco smoke influencing reporting by younger subjects. This is highly speculative as to potential to alter effect estimates

related to childhood exposures. The new meta-analysis conducted by OEHHA staff and included in the revised document supports ETS exposure as causative in both young child and older child asthma. The data also is consistent with studies of older children finding a less pronounced impact on asthma compared to early childhood because the exposure measurement is less precise. This is the result of questions that ask more or less "is the child exposed to ETS" at the time of the study. In early childhood this is a closer estimate of lifetime exposure than in late childhood.

The comment also notes that wheezing, a hallmark symptom of asthma, was not reported as significantly associated with ETS exposure. This is true, but other hallmark symptoms of asthma, such as attacks of shortness of breath and breathing difficulties during exercise were associated with ETS.

Comment 14:

Janson et al., 2001

This cross-sectional study aimed to evaluate the effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey. The study included 7882 adult (age 20-48) never smokers from 36 centers in 16 countries. The authors report, "…passive smoking in the workplace was significantly associated with all types of respiratory symptoms and current asthma. No significant association was found between passive smoking and total serum IgE." The authors conclude that although, "passive smoking is common, the prevalence varies widely between different countries." The study reports, "passive smoking increased the likelihood of experiencing respiratory symptoms and was associated with increased bronchial responsiveness."

Cal/EPA 2003

"Compared with no ETS exposure, <u>any</u> ETS exposure at home or work was not associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84; 1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25; 2.88). There was no

apparent impact of home exposure (OR 1.14; 95% CI 0.68; 1.90). These apparently discrepant results could be explained by the method of ETS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence with a smoker may not always reflect domestic ETS exposure (Eisner et al., 2001), use of this exposure measure could attenuate the effect estimate for home ETS exposure."

"The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea (nocturnal or exertional). In these instances, workplace ETS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. An exposure-response relationship was noted for all respiratory symptoms, but not clearly for asthma. Furthermore, both home and workplace ETS exposure were associated with greater bronchial hyper-responsiveness (assessed by methacholine challenge). Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between ETS exposure and self-reported asthma."

Heck et al. *Comments*

The study design was unblinded with "interview-led questionnaires." The percentage of cases classifiable as self-reported "adult-onset" asthma is unclear. Asthma was self-reported and subjects were not queried as to their age at onset and whether their reported asthma was physician-diagnosed. Thirty-six centers were studied, while only one used biomarkers of smoke exposure to validate nonsmoker status or ETS levels. The authors' abstract statement that "…passive smoking in the workplace as significantly associated with all types of respiratory symptoms and current asthma…" is inconsistent with the 95% confidence interval about the odds ratio and indicates a lack of statistical significance (odds ratio 1.90; 95% CI 0.90-2.88).

No significant association was seen between asthma and overall ETS exposure, asthma and household ETS exposure and ETS and total serum IgE. Reduction in lung function was not statistically significant in "ETS-exposed" participants.

In addition, the authors note a number of study limitations including cross-sectional design, possibility of recall bias and reliance on self-reported exposure. Cross-sectional studies are not appropriate as a basis for the development of inferences of causation.

Response:

The odds ratio for passive smoking and the risk of current asthma was 1.90 (95% CI 1.25 to 2.88) – see Table 2. This controlled for a large variety of potential confounding variables, including age, sex, parental smoking, sensitization to common aeroallergens, total IgE, and study center.

While there was no significant association seen between total serum IgE and ETS exposure, not all asthmatics have IgE elevation and not all persons with IgE elevation have asthma.

The statement about reduction in lung function not being statistically significant is inaccurate. Table 5 shows an exposure-response trend between daily passive smoke exposure duration and reduction of FEV1 (p=0.01 for trend; the highest exposure group had a statistically significant mean reduction of FEV1 of 63 ml compared to the unexposed group.

Of course, every study has limitations. The strengths of this study are its size, quality, and population based sampling (European Community Respiratory Health Study).

Comment 15:

Flodin et al., 1995

A population-based case-control study from semi-rural Sweden evaluated smoking as a possible determinant of "adult-onset" asthma (age ≥ 20 yrs), controlling for other factors such as air pollution at work, dwelling conditions, and atopy. The authors compared 79 cases of asthma, diagnosed between ages 20 and 65, with 304 randomly drawn population controls of similar age from the same area as the cases. A questionnaire was used to collect information on smoking habits, occupational exposures, dwelling conditions, various suspect allergenic exposures, and atopy. The authors note, "those who had smoked for 3 years or more, present or past, were at increased risk for bronchial asthma (adjusted odds ratio = 1.9; 95% confidence interval = 1.1-3.3)." Exposure to ETS at work involved a slightly greater but statistically insignificant risk (OR 1.5; 95% CI 0.8-2.5).

Cal/EPA 2003

"A population-based case-control study from semi-rural Sweden evaluated ETS exposure as a risk factor for adult onset asthma (≥age 20 years). During a 9 month period, cases were identified from all persons filling a prescription for beta-agonist medications in two communities. The diagnosis of asthma was confirmed by a pulmonary specialist. Controls were randomly selected from a general population register and matched to cases

by age (of asthma diagnosis), gender, and community. ETS exposure at both home and work was assessed by written questionnaire, which was defined as exposure for at least 3 years prior to the age at asthma diagnosis (or comparable age for controls). Workplace ETS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8-2.5), but the confidence interval did not exclude no relationship. Exposure to ETS at home was not associated with a greater risk of asthma (OR 0.9; 95% CI 0.5-1.5)."

Heck et al. *Comments*

This study examines 79 persons with asthma who were 20-65 years at diagnosis. The study does not appear to separately examine smokers and nonsmokers. The risk for adult asthma in association with three years of self-reported ETS exposure at work was nonsignificant (adjusted OR = 1.5, 95% CI = 0.8-2.5).

At home the risk was actually less than 1.0 (OR = 0.9, 95% CI =0.5-1.9) for ETS-exposed subjects. Due to the reported lack of a statistically significant association and apparent failure to separately examine smokers and nonsmokers, this study does not support a causal association between ETS exposure and "adult-onset" asthma.

Response:

The study controlled for the potential confounding effect of smoking. Heck is alluding to effect-modification, which is a different issue. This is an overly simplistic argument – the risk was elevated and most of the 95% CI was on the side of increased risk. The small sample size resulted in decreased precision of the OR estimate, which is a limitation, but not a fatal one.

As regards the statement that the at home risk was actually less than one, this statement is misleading as the CI is quite wide and is also consistent with a near-doubling of the risk of asthma.

Comment 16:

Thorn et al., 2001

A Swedish population based case-control study examined self-reported exposures to mold and ETS in the home environment and the risk of "adult-onset" asthma. The study was performed in a random population sample (n=15,813), aged 20-50 years. The adult

onset asthma cases for the study included subjects self reporting "physician-diagnosed" asthma (n=174). Randomly selected referents (n=870) were chosen from the whole population sample. Exposures in the home environment, asthma, respiratory symptoms, smoking habits, and atopy were obtained from a comprehensive mailed questionnaire. Authors reported, "increased adjusted OR for asthma were associated with exposure to molds (OR 2.2, 95% CI 1.4-5.5) ETS (OR 2.4, 95% CI 1.4-4.1) and the presence of a wood stove (OR 1.7, 95% CI 1.2-2.5)."

Cal/EPA 2003

"A Swedish population based case-control study examined the impact of ETS exposure on "adult-onset" asthma (age $\geq$ 16 yrs). The investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, ETS exposure was associated with a greater risk of "adult-onset" asthma (OR 2.4; 95% CI 1.4-4.1). This increased risk was observed only among never smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2.0-11.6) than females (OR 1.5; 95% CI 0.8-3.1)."

Heck et al. *Comments*

The relative risks and confidence intervals for ETS (OR 2.4, 1.4-4.1) and mold (OR 2.2, 1.4-3.5) are so similar it raises the possibility that the two exposures are co-existent. The attribution of adult onset asthma to ETS may actually be confounded by mold which may or may not be evident to the subject.

When the relative risks for males and females are reported separately, the relative risk for females for ETS and adult asthma is non-significant, 1.5 (0.8-3.1).

The authors throw out data by starting with 251 cases of physician diagnosed asthma, then reducing the final subject number to 174 by arbitrarily reviewing only the period "between 1980 and 1994" purportedly to reduce recall bias. No report of the relative risks using the whole sample is given.

When all self-reported asthmatic symptoms are included in addition to self-reported physician diagnosed adult asthma, the risk becomes non-significant at 1.7 (1.0-2.8).

The authors note the possibility of both under- and over-reporting of ETS exposure in their study design.

Response:

The similarity of two odds ratios does not imply anything about the correlation between two predictor variables. In fact, examination of Table 2 shows that the prevalence of

exposure to ETS and mold was quite different. For example, 47.8% of cases indicated exposure to ETS, whereas only 17.8% indicated mold exposure. There is no evidence that ETS exposure and mold are correlated.

The comment notes that relative risks for females alone is nonsignficiant. This is a statistical power issue, not a substantive issue.

The comment also notes that the authors "threw out data". The authors clearly describe their rationale for limiting the universe of cases to those who reported new-onset asthma during the period between 1980 and 1994, to enhance the likelihood of accurate reporting.

The comment notes that when all self-reported asthmatic symptoms are included in addition to self-reported physician diagnosed adult asthma, the risk becomes nonsignificant. The main outcome is incident adult-onset asthma, which was statistically significant.

Comment 17:

Hu et al., 1997

Asthma and related factors were evaluated in a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. Childhood ETS exposure to parental smoking was determined by parental reports. Seven years later during young adulthood, self-reported physician diagnosed asthma was determined using a written questionnaire. Family history was strongly associated with subjects' asthma (OR=3.1, 95% CI 2.4-4.5 for self reported physician- diagnosed asthma; OR=3.3, 95% CI 2.4-4.5 for current asthma). Exposure to parental smoking during childhood was significantly associated with self reported physician-diagnosed asthma (OR=2.9, 95% CI 1.6-5.6) and current asthma (OR=3.3, 95% CI 1.7-6.4). Also, self-reported mold growth at home was significantly associated with asthma (OR=2.0, 95% CI 1.2-3.2).

Cal/EPA 2003

"Hu et al. evaluated a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. At baseline, ETS exposure status was determined by parental reports of personal smoking. During young adulthood (seven years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental ETS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline (< one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in young adulthood (OR 1.8; 95% CI 1.1-3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1-2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma seven years later."

Heck et al. *Comments*

In this study, the age of onset for the reported asthma cases was not determined. Thus, the relevance of the findings to adult asthma onset is unclear.

Also, in this study, like others, there is a potential selection bias in selecting the cohort for study in that "…These subjects originally participated in a school-based smoking prevention study in 1986." The possibility of the unblinded subject correlating the current asthma "yes" or "no" question with the previous smoking cessation program cannot be excluded.

Response:

It is true that asthma onset would have occurred between the 7th grade, when most people are 12-13 years old, and the seven year follow-up, which would have occurred at 19-20 years old for most subjects. Consequently, asthma onset would have occurred during adolescence or early adulthood, which is best classified as "adult-onset" for most study subjects. In addition, there is no evidence that asthma that begins in adolescence vs. early adulthood is biologically different.

It is difficult to understand how participation in a school-based smoking prevention program could have introduced bias, selection bias or otherwise.

Comment 18:

Greer *et al*., 1993; McDonnell *et al*., 1999

A longitudinal cohort study of 3,914 adult non-smoking Seventh-Day Adventists living in California evaluated, by questionnaire, ETS exposure and the incidence of self-reported physician diagnosed asthma during a 15 year period. The authors reported the 10-year result (Greer et al., 1993) as relating asthma to occupational and ambient air pollution in nonsmokers. Similarly, the 15-year cohort follow-up (McDonnell et al., 1999) examined the incidence of asthma in nonsmokers with the long term ambient ozone concentrations. The Greer et al. (1993) study found: 1) ETS exposure significantly associated with the development of asthma (RR = 1.45; CI = 1.21 to 1.75), 2) airways obstructive disease before age 16 related to a marked increase risk (RR = 4.24, CI 4.03 to 4.45), and 3) an increased risk of asthma significantly associated with increased ambient concentration of ozone exposure in men (R = 3.12, CI = 1.61 to 5.85), but not in women.

The study by McDonnell et al. (1999) suggested that long-term exposure to ambient ozone is associated with development of asthma in adult males. The only ETS exposure associated with asthma was in nonsmoking females only, with weak relative risk, 1.21 (CI=1.04-1.39).

Cal/EPA 2003

"As reported in the 1997 Cal/EPA report, duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI= 1.2-1.8). Since the 1997 Cal/EPA report, longer-term follow-up of the cohort has been reported. At 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI= 1.04-1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma."

Heck et al. *Comments: Greer et al., 1993*

The representativeness of the Seventh Day Adventist (SDA) cohort to the broader California population is questionable. Furthermore, the prohibition of smoking by SDA church doctrine may increase the likelihood of smoker misclassification bias in this unique cohort. The ETS exposure is self-reported. The reported relative risk for adult asthma and ETS is very weak, RR 1.45 (CI =1.21-1.80).

The subject numbers of incident asthma cases are small, that is, N =51 for females and N = 27 for males.

Only 13% of the potential respondents did not answer the questionnaire, but the final cohort is 2/3 female. Whether more females were initially queried is unknown. The average age at time of enrollment is relatively high, that is, 56.5. The plausibility that

after a lifetime of ETS exposure without developing asthma, asthma is then induced after the age of 56.5 is questionable.

Heck et al. *Comments: McDonnell et al., 1999*

ETS was associated with asthma in nonsmoking females only, with a weak relative risk, 1.21 (1.04-1.39). In addition, the authors note that, "Misclassification of asthma status may have been greater in females than males," and that, "The degree of obstruction represented by FEV_1/FVC was considerably larger in males than females (Table 2), and only 27% of the new female cases reported use of asthma medication compared to 61% of the males." Therefore, the reported statistically significant ETS/female association is not consistent with the study's clinical observations.

Response:

This group of Seventh Day Adventists is comprised largely of non-smokers, which makes them an ideal cohort to study the effects of indoor or outdoor air pollution. There is no available evidence that their religious practices reduce the generalizability of these results.

A 45% increase in risk in an assessment that was adjusted for important confounders has major implication for disease prevalence and population impacts for a common disease such as asthma. Strong associations are neither necessary nor sufficient for causality and weakness is neither necessary nor sufficient for absence of causality (Rothman and Greenland 1998).

Comment 19:

Cal/EPA 2003 paragraph summarizing asthma induction discussion

"There is no "gold standard" for defining asthma in epidemiological research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma (McWhorter et al., 1989; Toren et al., 1993). Respondents' reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma (Toren et al., 1993). Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney et al., 1989)."

Heck et al. Comments

As shown in Table 1, there is significant heterogeneity in application of diagnostic criteria across the nine studies and in the general ETS asthma literature. While no diagnostic "gold standard" may be available, certainly minimum diagnostic standards should be used, as there is the possibility of a self-reported misdiagnosis especially with "adult-onset" asthma. Other conditions, for example the side effects of various drugs, could lead to a misdiagnosis. In general, actual physician diagnosis is superior to self-report.

Cal/EPA is correct in stating that there is no universally-accepted and entirely objective definition of asthma in epidemiology. Yet while Cal/EPA emphasizes the possibility that self-reported "asthma-like" symptoms may under-represent true asthma incidence, a more scientifically objective view would acknowledge that an imprecise definition of diseases would just as likely lead to over-reporting of common viral or bacterial respiratory infections as "asthma". Cal/EPA should revise its draft wording to fairly and objectively consider this reality.

Response:

While actual physician diagnosis may be a better measure of asthma than self-report of a physician's diagnosis as a measure of asthma, it is not feasible to do this in large-scale epidemiologic studies. Furthermore, as noted in earlier responses, many studies have demonstrated that self-reported physician diagnosis of asthma is a relatively robust way to ascertain asthmatic status.

Comment 20:

Conclusions

In summary, the nine new studies cited in the Cal/EPA 2003 document comprise: five foreign studies performed in populations and environments differing substantially from those of California; two studies of a Seventh Day Adventist cohort having numerous lifestyle differences from those of typical Californians;

Response

Indeed, the consistency of findings across samples drawn from populations around the world supports the ETS-asthma association.

Comment 21:

Four cross-sectional studies inappropriate for the development of inferences of causality; eight studies lacking a complete medical confirmation of asthma diagnosis; and a variety of additional deficiencies discussed above and itemized in accompanying Tables 1 and 2. A number of the studies represented by Cal/EPA as demonstrating an association between ETS and asthma development did not in fact report consistent statistically significant associations.

The Cal/EPA draft conclusion that ETS exposure is causally-related to the induction of "adult-onset" asthma cannot be justified by scientific standards. No other authoritative scientific bodies around the world have rendered a similar judgement upon examination of available epidemiological data. The simplistic conclusion that exposure to ETS is causally related to a complex, multifactoral, and incompletely understood disease condition such as "adult-onset" asthma is not supported by a compelling body of extant epidemiological data or supportive temporal and mechanistic data and should be withdrawn by Cal/EPA in its revision of the draft 2003 report.

Response:

Two prospective cohort studies (Hu and the Adventist Health Study,) support the association between ETS exposure and adult-onset asthma. The Adventist Health Study clearly studied incident, adult-onset asthma. Three population-based case control studies (Flodin, Thorn and Jaakola) and four cross-sectional studies reviewed in this document provide supporting evidence of an association between ETS exposure and adult-onset asthma. One case-cross over study (Eisner) and two cohort studies (Withers, Strachan) support an association between ETS exposure and adult-onset wheezing.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger et al., 1994), number of

smokers in the environment, (Leuenberger et al., 1994; Hu et al., 1997) duration of exposure to smokers (Leuenberger et al., 1994; Iribarren et al., 2001; Janson et al., 2001; Kunzli et al., 2000), duration of working with a smoker (Greer at el., 1993; McDonnell et al., 1999), measured nicotine levels (Eisner et al., 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola et al., 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset and exacerbation.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin 1995, Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999), or a defined period prior the development of asthma-like symptoms (Withers 1998, Strachan 1996). In these studies, exposure to ETS clearly predated the development of asthma.

In interpreting these epidemiologic studies, a critical issue is whether the observed association between ETS exposure and adult asthma could be explained by confounding factors. ETS exposure has been associated with younger age, female gender, non-white race, lower education, lower income, blue-collar occupation, and personal cigarette smoking (Iribarren et al., 2001; Hole et al., 1989; Mannino et al., 1997; Sippel et al., 1999). Many of these factors have also been associated with an increased prevalence of asthma and asthma-related morbidity (Mannino et al, 1998). All of the studies considered and controlled for potentially confounding variables. Overall, the observed

relationship between ETS exposure and asthma appears to be robust and not explained by confounding.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a deleterious causal effect of ETS exposure on adult asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (Cal/EPA, 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function. (Hole et al., 1989; Comstock et al., 1981; Ng et al., 1993; Masi et al., 1988; O'Connor et al., 1987; Xu and Li, 1995; Schilling et al., 1977; Kauffmann et al., 1989; Brunekreef et al., 1985; Abbey et al., 1998; Carey et al., 1999; Jaakkola et al., 1995; Dimich-Ward et al., 1998;Eisner et al., 1998; Eisner, 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association. In sum, examination of the Hill criteria supports a causal association between ETS exposure and adult-asthma onset.

References in Comments

Boushey, H.A., Corry, D.B., Fahy, J.V., 2000. Asthma, Chapter 39 in *Textbook of Respiratory Medicine*, Volume 2, Third Edition, J.A. Murray, J.A. Nadel (eds.), W.B. Saunders, Philadelphia, pp. 1247-1289.

California Environmental Protection Agency. 2003. Public Review Draft). Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, Part B: Health Effects. Chapter 6. Respiratory Health Effects, pp 1-104.

Dayal, H.H., Khuder, S., Sharrar, R., Trieff, N., 1994. Passive smoking in obstructive respiratory disease in an industrialized urban population. *Environ Res* 65(2):161-71.

Flodin, U., Jonsson, P., Ziegler, J., Axelson, O., 1995. An epidemiologic study of bronchial asthma and smoking. *Epidemiology* 6(5):503-5.

Greer, J.R., Abbey, D.E., Burchette, R.J., 1993. Asthma related to occupational and ambient air pollutants in nonsmokers. *J Occup Med* 35(9):909-15.

Hoffjan, S., Nicolae, D., Ober, C., 2003. Association studies for asthma and atopic diseases: a comprehensive review of the literature. *Respiratory Research* 4(1):14.

Hu, F.B., Persky, V., Flay, B.R., Zelli, A., Cooksey, J., Richardson, J., 1997. An epidemiological study of asthma prevalence and related factors among young adults. *J Asthma* 34(1):67-76.

IOM (Institute of Medicine), 2000. Clearing the Air: Asthma and Indoor Air Exposures. National Academy Press, Washington, DC.

Iribarren, C., Friedman, G.D., Klatsky, A.L., Eisner, M.D., 2001. Exposure to environmental tobacco smoke: association with personal characteristics and self-reported health conditions. *J Epidemiol Community Health* 55(10):721-8.

Janson, C., Chinn, S., Jarvis, D., Zock, J.P., Toren, K., Burney, P., 2001. Effect of passive smoking on respiratory symptoms, bronchial responsivemess, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. *Lancet* 358(9299):2103-9.

Jenkins, C., Costello, J., and Hodge,L., 1999. Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. *British Medical Journal* 328 (21 February):434-437.

Kronqvist, M., Johannsson, E., Perhage, G., Johannsson, S.G., van Hage-Hamsten, M., 1999. Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. *Allergy* 54(11):1142-9.

Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B, 2001. Enviromental tobacco moke exposure during childhood is associated with increased prevalence of asthma in adults. *Chest* 120(3):711-7.

Lehrer, S.B., Rando, R.J., and Lopez, M., 1999. The effects of environmental tobacco smoke on asthma: studies with a dynamic exposure chamber. In *Asthma: Causes and Mechanisms of an Epidemic Inflammatory Disease*, edited by T. Platts-Mills, Boca Raton, Florida: Lewis Publishers.

Leuenberger, P., Schwartz, J., Ackermann-Liebrich, U., Blasér, K., Bolobnini, G., Bongard, J.P., *et al*. 1994. Passive smoking exposure in adults and chronic respiratory symptoms (SALALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am J Respir Crit Care Med* 150(5 Pt 1):1222-8.

McDonnell, W.F., Abbey, D.E., Nihino, N., Lebowitz, M.D., 1999. Long-term ambient ozone concentraitonn and the incidence of asthma in nonsmoking adults: the AHSMOG study. *Environ Res* 80(2 Pt 1):110-21.

Ng T.P., Hui K.P., Tan W.C., 1993. Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. *J Epidemiol Community Health* 47(6):454-8.

Robbins A.S., Abbey D.E., Lebowitz M.D., 1993. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int J Epidemiol* 22(5):809-17.

Sama, Susan R., et al., Environ Health: A Global Access Science Source 2 :10 (2003).

Smith, C. J., Sears, S. B., Walker, J.C., and DeLuca P.O. 1992. Environmental tobacco smoke: Current assessment and future directions. *Toxicologic Pathology*. 20(2): 289-305.

Thorn J, Brisman J, Toren K (2001). "Adult-onset" asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy* 56(4:287-92.

Tredaniel, J., Boffetta, P., Saracci, R., Hirsch, A., 1994. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur Resp J* 7:173-.

Table 1. Summary of Exposure and Risk Factors: Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	Country	Study Type And Year conducted	Variables Tested	Population	Smoking Status Smoker vs Nonsmoker	Smoking status confirmed by lab test	Exposure to ETS	Known Home exposures/ confounders considered	Known Occupational exposures/ con-founders considered
Kronqvist et al., 1999	Sweden	Cross-sectional 1996	Risk Factors	Population based 15-65 years dairy farmers (n=461)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire (especially for farmers)
Iribarren et al., 2001	Northern California USA	Cross-sectional 1979-1985	ETS esposure / personal characteristics	Lg health plan participants Never smokers 16,524 men (15-89) 26,197 women (15-105)	Questionnaire	No Subset only	Questionnaire (year collected not clear)	Questionnaire "lifestyle" factors	Questionnaire
Larsson et al., 2001	Orebro, Sweden	Population 1995-1996	ETS childhood exposure	Total of 8008 random inhabitants (15-69)	Questionnaire	No	Questionnaire	Some	Questionnaire
Janson et al., 2001	Europe	Cross-sectional 1990-1994	Passive smoking	7882 adults from 36 centres in 16 countries 3486 men; 4396 women (age 20-48) "never-smokers"	Questionnaire Self report	No	Questionnaire	Interview/ questionnaire "lifestyle" factors	Questionnaire Semi quant estimate from matrix of 350 occup. groups. Noted as none, low or high.
Flodin et al., 1995	Sweden	Case control 1990	Smoking	Population based 79 (20-65 yrs) w/ asthma 304 controls (age/sex)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Thorn et al., 2001	Alvsborg, Sweden	Retrospective case control 1994	Mold or ETS	Population 15,813 (age 20-50)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Hu et al., 1997	LA and San Diego California USA	Cohort 1993	Asthma related factors	n=2041 age 20-22	Questionnaire Self report	No	Questionnaire	yes	Not noted
Greer et al., 1993	SF, LA or San Dieo California USA	Long term prospective Cohort 1977; 1987	Occupational & ambient air pollution	n=3914 Adult ($\geq$25 yrs) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Not noted	1987 included as part of questionnaire
Mc Donnell et al., 1999	SF, LA or San Dieo California USA	Longitudinal prospective cohort 1977; 1987; 1992	Long term ambient ozone concentration	n=3091 Adult (age 27-87) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Questionnaire	Questionnaire

Table 2. Criteria for Asthma Diagnosis : Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	Author Defined Asthma Symptoms	Questionnaire	Self reported Asthma or symptoms of asthma	Self Reported Physician Diagnosed	Physician Diagnosed Asthma	Medical Confirmation of Asthma symptoms
Kronqvist et al., 1999	History of episodic shortness of breath, wheezing, & breathing difficulties	yes	yes	no	yes	Allergic Disease Physician SPT (13 allergens) RAST (blood) Lung function test
Iribarren et al., 2001	Hay fever/ Asthma	yes	yes Hay fever/ Asthma	yes	no	Not noted
Larsson et al., 2001	Not noted	Yes – Developed from the British Medical Research Council questionnaire	Questions on many respiratory symptoms	yes	no	no
Janson et al., 2001	Not noted	Screening questionnaire Interview led questionnaire	Questions on many respiratory symptoms	no	no	Blood tests total and specific IgE, spirometry, methacholine challenge
Flodin et al., 1995	American Thoracic Society	American Thoracic Society	Beta-agonist users	no	Selected cases confirmed with doctor	Examined by lung specialist
Thorn et al., 2001	Not noted	1. Screening questionnaire 2. Mailed comprehensive questionnaire	Questions on many respiratory symptoms	yes	no	no
Hu et al., 1997	Not noted	questionnaire	yes	yes	no	no
Greer et al., 1993	Not noted	Questionnaire developed by British Medical Research Council	Questions on many respiratory symptoms	yes	no	1987 "cases" – 1990 medical record/physician confirmation
Mc Donnell et al., 1999	American Thoracic Society	American Thoracic Society	Questions on many respiratory symptoms	yes	no	Lung function testing Spirometry Peak expiratory flow (PEF)

References in Responses

Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL (1998).. Long-term particulate and other air pollutants and lung function in nonsmokers. American Journal of Respiratory and Critical Care Medicine 158:289-98.

Abramson M, Kutin J, Czarny D, Walters EH (1996). The prevalence of asthma and respiratory symptoms among young adults: is it increasing in Australia? J Asthma 33:189-96.

Basagana X, Sunyer J, Kogevinas M, Zock JP, Duran-Tauleria E, Jarvis D, Burney P, Anto JM (2004). Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. Am J Epidemiol 160:178-88.

Benowitz NL (1999). Biomarkers of environmental tobacco smoke exposure. Environmental Health Perspectives 107 Suppl 2:349-55.

Bjornsson E, Plaschke P, Norrman E, Janson C, Lundback B, Rosenhall A, Lindholm N, Rosenhall L, Berglund E, Boman G (1994). Symptoms related to asthma and chronic bronchitis in three areas of Sweden. Eur Respir J 7:2146-53.

Brunekreef B, Fischer P, Remijn B, van der Lende R, Schouten J, Quanjer P (1985). Indoor air pollution and its effect on pulmonary function of adult non-smoking women: III. Passive smoking and pulmonary function. International Journal of Epidemiology 14:227-30.

Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T (1989). Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. European Respiratory Journal 2:940-5.

Burney PG, Luczynska C, Chinn S, Jarvis D (1994). The European Community Respiratory Health Survey. Eur Respir J 7:954-60.

Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD (1991). Characteristics of asthma among elderly adults in a sample of the general population. Chest 100:935-42.

Cal/EPA (1997). Health effects of exposure to environmental tobacco smoke. California Environmental Protection Agency, Sacramento, CA.

Carey IM, Cook DG, Strachan DP (1999). The effects of environmental tobacco smoke exposure on lung function in a longitudinal study of British adults. Epidemiology 10:319-26.

Coghlin J, Hammond SK, Gann PH (1989). Development of epidemiologic tools for measuring environmental tobacco smoke exposure. American Journal of Epidemiology 130:696-704.

Comstock GW, Meyer MB, Helsing KJ, Tockman MS(1981). Respiratory effects on household exposures to tobacco smoke and gas cooking. American Review of Respiratory Disease 124:143-8.

Coultas DB, Peake GT, Samet JM (1989). Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. American Journal of Epidemiology 130:338-47.

Coultas DB, Samet JM, McCarthy JF, Spengler JD (1990). A personal monitoring study to assess workplace exposure to environmental tobacco smoke. American Journal of Public Health 80:988-90.

Cummings KM, Markello SJ, Mahoney M, Bhargava AK, McElroy PD, Marshall JR (1990). Measurement of current exposure to environmental tobacco smoke. Archives of Environmental Health 45:74-9.

Cunningham J, O'Connor GT, Dockery DW, Speizer FE (1996). Environmental tobacco smoke, wheezing, and asthma in children in 24 communities. American Journal of Respiratory and Critical Care Medicine 153:218-24.

Daisey JM (1999). Tracers for assessing exposure to environmental tobacco smoke: what are they tracing? Environmental Health Perspectives 107 Suppl 2:319-27.

de Marco R, Pattaro C, Locatelli F, Svanes C (2004). Influence of early life exposures on incidence and remission of asthma throughout life. J Allergy Clin Immunol 113:845-52.

Dimich-Ward H, Lawason J, Chan-Yeung M (1998). Work shift changes in lung function in bar workers exposed to environmental tobacco smoke. American Journal of Respiratory and Critical Care Medicine 157:A505.

Dodge RR, Burrows B (1980). The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. American Review of Respiratory Disease 122:567-75.

Dodge R, Cline MG, Burrows B (1986). Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. American Review of Respiratory Disease 133:981-6.

ECRHS (1995). Prevalence of asthma and asthma symptoms in a general population sample from northern Italy. European Community Respiratory Health Survey--Italy. Allergy 50:755-9.

Eisner MD, Smith AK, Blanc PD(1998). Bartenders' respiratory health after establishment of smoke-free bars and taverns [see comments]. Jama 280:1909-14.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD (2001). Measurement of environmental tobacco smoke exposure among adults with asthma. Environmental Health Perspectives 109:809-14.

Eisner MD (2002). Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: impact on the general population and adults with current asthma. Environ Health Perspect 110:765-70.

Emmons KM, Marcus BH, Abrams DB, Marshall R, Novotny TE, Kane ME, Etzel RA (1996). Use of a 24-hour recall diary to assess exposure to environmental tobacco smoke. Archives of Environmental Health 51:146-9.

Greer JR, Abbey DE, Burchette RJ (1993). Asthma related to occupational and ambient air pollutants in nonsmokers. Journal of Occupational Medicine 35:909-15.

Hoffjan S, Nicolae D, Ober C (2003). Association studies for asthma and atopic diseases: a comprehensive review of the literature. Respiratory Research 4:14.

Hole DJ, Gillis CR, Chopra C, Hawthorne VM (1989). Passive smoking and cardiorespiratory health in a general population in the west of Scotland [see comments]. Bmj (Clinical Research Ed.) 299:423-7.

Hu FB, Persky V, Flay BR, Richardson J (1997). An epidemiological study of asthma prevalence and related factors among young adults. Journal of Asthma 34:67-76.

Iribarren C, Friedman GD, Klatsky AL, Eisner MD (2001). Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 55:721-8..

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P (1995). Passive smoking and evolution of lung function in young adults. An 8-year longitudinal study. Journal of Clinical Epidemiology 48:317-27.

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P (1996). Effect of passive smoking on the development of respiratory symptoms in young adults: an 8-year longitudinal study. Journal of Clinical Epidemiology 49:581-6.

Jaakkola MS, Jaakkola JJ (1997). Assessment of exposure to environmental tobacco smoke. European Respiratory Journal 10:2384-97.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358:2103-9.

Jarvis D, Lai E, Luczynska C, Chinn S, Burney P (1994). Prevalence of asthma and asthma-like symptoms in young adults living in three east Anglian towns. Br J Gen Pract 44:493-7.

Jenkins C, Costello J, Hodge L (2004). Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. British Medical Journal 328:434-437.

Kauffmann F, Dockery DW, Speizer FE, Ferris BG, Jr (1989). Respiratory symptoms and lung function in relation to passive smoking: a comparative study of American and French women. International Journal of Epidemiology 18:334-44.

Kunzli N, Schwartz J, Stutz EZ, Ackermann-Liebrich U, Leuenberger P (2000). Association of environmental tobacco smoke at work and forced expiratory lung function among never smoking asthmatics and non-asthmatics. The SAPALDIA-Team. Swiss Study on Air Pollution and Lung Disease in Adults. Sozial- und Praventivmedizin 45:208-17.

Lehrer SB, Rando RJ, Lopez M (1999). The effects of environmental tobacco smoke on asthma: studies with a dynamic exposure chamber. In: Asthma: Causes and Mechanisms of an Epidemic Inflammatory Disease (Platts-Mills T, ed). Boca Raton, FL: Lewis Publishers, pp. 155-195.

Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, Brutsche M, et al. (1994). Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team [see comments]. American Journal of Respiratory and Critical Care Medicine 150:1222-8.

Mannino DM, Siegel M, Rose D, Nkuchia J, Etzel R (1997). Environmental tobacco smoke exposure in the home and worksite and health effects in adults: results from the 1991 National Health Interview Survey. Tobacco Control 6:296-305.

Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E, Kang DS (1998). Surveillance for asthma--United States, 1960-1995. Morbidity and Mortality Weekly Report. Cdc Surveillance Summaries 47:1-27.

Masi MA, Hanley JA, Ernst P, Becklake MR (1988). Environmental exposure to tobacco smoke and lung function in young adults. American Review of Respiratory Disease 138:296-9.

McDonnell WF, Abbey DE, Nishino N, Lebowitz MD (1999). Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. Environmental Research 80:110-21.

MMWR (2004). Cigarette smoking among adults--United States, 2002. Morb Mortal Wkly Rep 53:427-31.

Neukirch F, Pin I, Knani J, Henry C, Pison C, Liard R, Romazzini S, Bousquet J (1995). Prevalence of asthma and asthma-like symptoms in three French cities. Respir Med 89:685-92.

Ng TP, Hui KP, Tan WC (1993). Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. Journal of Epidemiology and Community Health 47:454-8.

O'Connor GT, Weiss ST, Tager IB, Speizer FE (1987). The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults [published erratum appears in Am Rev Respir Dis 1987 Aug;136(2):532]. American Review of Respiratory Disease 135:800-4.

O'Connor TZ, Holford TR, Leaderer BP, Hammond SK, Bracken MB (1995). Measurement of exposure to environmental tobacco smoke in pregnant women. American Journal of Epidemiology 142:1315-21.

Rothman, K. J. and Greenland, S. Causation and causal inference. Rothman, K. J. and Greenland, S. Modern Epidemiology. 2-28. 98. Philadelphia, USA, Lippincott-Raven publishers.

Schilling RS, Letai AD, Hui SL, Beck GJ, Schoenberg JB, Bouhuys A (1977). Lung function, respiratory disease, and smoking in families. American Journal of Epidemiology 106:274-83.

Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML (1999). Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest 115:691-6.

Toraen K, Brisman J, Jearvholm B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review [see comments]. Chest 104:600-8.

von Mutius, Erika Environmental factors influencing the development and progression of pediatric asthma. Journal of Allergy & Clinical Immunology 109(6 Supplement), S525-S532. 2002.

Willemsen MC, Brug J, Uges DR, Vos de Wael ML (1997). Validity and reliability of self-reported exposure to environmental tobacco smoke in work offices. Journal of Occupational and Environmental Medicine 39:1111-4.

Xu X, Li B (1995). Exposure-response relationship between passive smoking and adult pulmonary function. American Journal of Respiratory and Critical Care Medicine 151:41-6